International Journal of Infectious Diseases 33 (2015) 191–195

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Epidemiological investigation of an outbreak of hepatitis A in rural China

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ARTICLE INFO

Article history:
Received 15 October 2014
Received in revised form 3 February 2015
Accepted 4 February 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Hepatitis A
Outbreak
Person-to-person transmission
Case–control study

SUMMARY

Objectives: This investigation was a response to an outbreak of hepatitis A in rural China in 2013. The objectives were to identify the pattern of transmission and the risk factors.
Methods: A probable case was defined as an individual in/nearby the village of the outbreak with jaundice and/or an elevation of serum alanine aminotransferase (at or above 80 IU/l) plus at least three of the following symptoms: fever (axillary temperature ≥37 °C), headache, nausea, vomiting, anorexia, or abdominal pain in the upper right quadrant, during the outbreak period (from June 1 to August 11, 2013). Using a case–control study design, we compared exposures to suspected food items, water, and close contact with a patient or case with asymptomatic infection between 22 cases and 32 controls.
Results: We identified 22 cases, including 15 symptomatic cases and seven with asymptomatic infections. All cases were aged <15 years. Household clustering was apparent (Chi-square = 4.69, $p < 0.05$). Contact with symptomatic cases or cases with an asymptomatic infection was a major risk factor (59.09% in cases and 25.00% in the controls: odds ratio (OR) 4.33, 95% confidence interval (CI) 1.17–16.68). A good hand-washing habit (at least once per day) was found in 45.45% of cases vs. 78.13% of controls (OR 0.23, 95% CI 0.06–0.88). The dose–response analysis showed that the daily frequency of hand-washing was inversely associated with infection (trend Chi-square = 5.35, $p = 0.021$). Person-to-person transmission was deduced from the epidemic curves and the transmission chain of symptomatic cases.
Conclusion: The pattern of transmission in this outbreak was person-to-person, and the transmission route was indicated to be fecal–oral. In addition to close contact, insufficient hand-washing was a risk factor. Strengthening the management of the rural environmental sanitation services and enhancing awareness in the household are key to preventing outbreaks of hepatitis A in the future.

1. Introduction

Hepatitis A virus (HAV) is a positive-strand RNA virus, classified within the genus *Hepatovirus* in the family *Picornaviridae*.[1] It is transmitted primarily via the fecal–oral route, either through the ingestion of contaminated food/water or through direct contact with patients or those with asymptomatic infections.[2] Hepatitis A outbreaks often remain 'silent' due to the asymptomatic nature of the majority of cases and the relatively long incubation period.[3] The majority of infections are asymptomatic in young children, whereas symptoms are more common in adults.[4] The average incubation period is 28 days (range 15–50 days), during which the patients are highly contagious regardless of the presence or absence of symptoms.[5] Infection confers lifelong immunity, and no chronic infection has been documented.[6] In China, the incidence of hepatitis A was estimated at slightly above 100/100 000 in the 1980s, but this number is most likely a gross underestimation due to incomplete reporting.[7] Following a period of economic growth and the implementation of hepatitis A vaccination,[8,9] the incidence in China was estimated to be 7.2/100 000 in 2004 and

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http://dx.doi.org/10.1016/j.ijid.2015.02.006

3.3/100 000 in 2009.[10] Hepatitis A antibody is positive in about three quarters of the population at 25 years of age,[11] and in over 90% at 30 years of age.[12] Therefore, the lower age group has become the focus population and is generally involved in hepatitis A outbreaks. There have been frequent reports of hepatitis A outbreaks in recent years.[13–16] In the majority of reported outbreaks, the patients were mainly adolescents, affected by the fecal–oral transmission route due to contamination of food/water with sewage. An outbreak with the fecal–oral transmission route due to close contact has rarely been reported.

On August 10, 2013, an outbreak of hepatitis A was reported in an economically disadvantaged area in southern China – Yujia Village, Xinjian County, Jiangxi Province. This village is located in the northern outskirts of the county. At the time of the outbreak the village consisted of 63 households and 246 residents. Each household has their own water supply from deep wells (typically 10 m in depth) at about 5 m distant from their private lavatories. The residents typically consume unboiled water. Ninety-three of the village residents were children aged <15 years. The village children often gather in crowds and groups, and are in close contact with each other. There is a primary school in the village, which enrolls school-aged children from Yujia Village as well as seven nearby villages. The school summer holidays started 40 days before the outbreak report (June 28). Drinking water and food are not provided in the school.

We conducted an epidemiological investigation to (1) identify the range of the outbreak, (2) identify the pattern of transmission, and (3) identify the risk factors. The results are reported below.

2. Materials and methods

2.1. Ethics statement

This investigation was undertaken in response to a public health emergency, and based on the Law of the People's Republic of China on the Prevention and Treatment of Infectious Diseases (http://www.gov.cn/ziliao/flfg/2005-08/05/content_20946.htm), formal ethical approval was not required. We started the interview, sampling, and vaccination process with the verbal informed consent of all participants or their guardians. Consent was recorded on the questionnaire using the participant's and/or guardian's signature. All participants were informed of their rights according to the law outlined above. We can confirm that all data, including all questionnaires and samples, were gathered in accordance with the 'Guideline for hepatitis A outbreak reports and investigation', issued by the Department of Health of Jiangxi Province, China. No additional data were acquired by the authors.

2.2. Surveillance and descriptive epidemiology

A suspected case was defined as any individual in/nearby the village with at least three of the following symptoms between June 1 and August 11: fever (axillary temperature $\geq$37 °C), headache, nausea, vomiting, anorexia, or abdominal pain in the upper right quadrant. A probable case was defined in the presence of jaundice and/or elevated serum alanine aminotransferase (more than twice the upper limit of normal or 80 IU/l) in a suspected case. A confirmed case was defined as a suspected or probable case who was positive for anti-HAV IgM. Asymptomatic infection was defined in a patient who was anti-HAV IgM-positive but with no symptoms, except for those with hepatitis A immunization in the past 12 months. Close contact was defined as an average duration of contact with an infectious case of at least 3 h per day in the past 2 months.

Cases were identified by (1) reviewing the medical records in all public hospitals throughout Xinjian County, (2) reviewing the medical records of seven private clinics in the villages bordering Yujia Village, (3) strengthening hepatitis A surveillance in Xinjian County, (4) reviewing the attendance records of the primary school (since May 1) and appropriate follow-up, (5) testing of anti-HAV IgM in all children (at <15 years of age) in the village and their main caregivers, and (6) examining hepatitis A vaccination records.

2.3. Case–control study

The case subjects included all confirmed cases and asymptomatic infection cases. As the case subjects were all under 15 years old, we carried out an examination of serum HAV IgM and HAV IgG in all children aged <15 years in the village. Control subjects were selected randomly from healthy village residents aged <15 years with both serum HAV IgM and HAV IgG negative. All cases and controls were interviewed face-to-face by the investigators using a uniform questionnaire that collected the following information: (1) age and gender, (2) clinical features (symptoms, onset, hospitalization records, etc.), (3) epidemiological characteristics (food/water intake, hand-washing habit, contact with known cases), and (4) history of hepatitis A infection and immunization. The time range of the confirmed cases for risk factor investigation was one maximum incubation period prior to their date of onset. The time range of controls and asymptomatic cases was based comparatively on the case group.

Age and gender were compared between the cases and controls using a Student's *t*-test and the Pearson Chi-square test. A Chi-square test for trend was also used to analyze the relationship between the frequency of hand-washing and the mobility of hepatitis A. We used a Chi-square test to estimate household clustering by comparing the observed distribution to the binomial distribution for random allocation of cases to households. Statistical analyses were carried out using Epi Info software (version 3.3.2). Statistical significance was defined as $p < 0.05$.

2.4. Immunological tests

Serum HAV IgM and HAV IgG were examined in all children aged <15 years in the village. Serum HAV IgG was also examined in 47 consenting adult residents.

2.5. Virological and bacteriological investigations

Representative samples from the water supplies (from five families with hepatitis A cases located in the east, south, west, north, and center of the village, respectively) were examined for the total coliform group and fecal coliform group. These five water samples and four snack food samples ('latiao', a common snack for children in the village) were also tested for hepatitis A viral RNA by PCR. All tests were conducted at the Virology Laboratory of Jiangxi Center for Disease Control and Prevention.

3. Results

3.1. Surveillance and descriptive epidemiology

By August 11, a total of 22 cases had been identified in the village (Yujia): 15 confirmed cases and seven cases of asymptomatic infection. All cases were children aged <15 years; their mean age was 8.5 years (range 1–14 years). The mean age was 9 ± 4.66 years and 8 ± 4.30 years in symptomatic cases and asymptomatic cases, respectively ($t = 0.9642$, $p = 0.3464$). The infection rate in children <15 years of age was 23.66% (22/93) (Table 1).

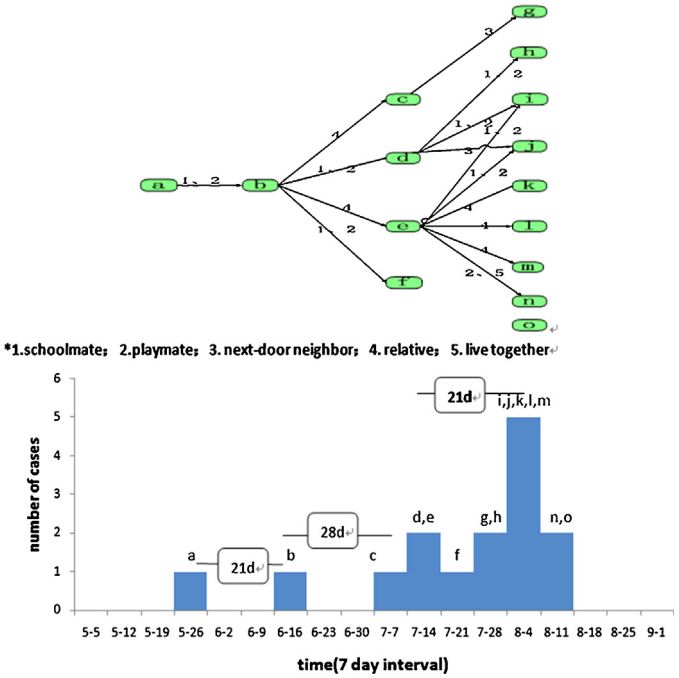

Figure 1. Epidemic curve and transmission chain for symptomatic cases (A common *x*-axis).

The 22 cases involved 16 households, with significant family clustering (Chi-square = 4.69, $p < 0.05$). The infection rate in those under 15 years of age was comparable between boys and girls (15/61 or 24.59% in boys vs. 7/32 or 21.88% in girls; Chi-square = 0.09, $p = 0.77$). No case (including suspected cases and probable cases) was reported outside the village.

Commonly reported symptoms included jaundice (66.67%), nausea (50%), anorexia (44.44%), abdominal pain in the right upper quadrant (44.44%), fever (21.43%), vomiting (16.67%), and headache (16.67%). Fifteen cases were hospitalized and all recovered uneventfully.

The epidemic curve presented four peaks, with an interval between the peaks of 3–4 weeks (Figure 1), indicating person-to-person transmission.[17] The first case was a 14-year-old boy who attended the village primary school. A detailed investigation of this boy was conducted, but no suspected source of infection, such as unboiled water, unclean food, or close contact with any suspected case was found. The onset was June 1. The second case presented 3 weeks later in a child who had been in close contact with the first case and attended the same school. The third peak included four cases; all had been in close contact with the second case as a playmate, schoolmate, or relative. All four cases presented about 4 weeks after the onset of the second case. The fourth peak occurred 3 weeks after the third peak; all had been in close contact with the cases involved in the third peak except case 'o'. The source of infection for case 'o' may have been an asymptomatic case, but this could not be verified.

The attendance log of the village primary school did not reveal a suspected source. The water supply system in the village is dispersed. The 22 cases used 16 of the private wells, and it would be unlikely that multiple wells were responsible for the outbreak within the limited time period. No party event was identified to have occurred in the past 2 months. The majority of snacks (latiao and popsicles) shared by the children were purchased outside the village, and these are very popular in the whole of Xinjian County. However, there was no case of hepatitis A in the other villages during the outbreak period. Based on the above, the person-to-person transmission hypothesis was put forward for further analysis.

3.2. Case–control study

The analysis included all 22 cases and 32 healthy controls. The mean age of cases was 8.5 ± 4.55 years and of controls was 10.5 ± 3.68 years ($t = -1.74$, $p = 0.09$). The gender ratio did not differ between cases (15 males and seven females) and controls (19 males and 13 females) (Chi-square = 0.43, $p = 0.51$). During the period June 1 to August 26, 59.09% (13/22) of cases had been in close contact with infectious cases compared to 25.00% (8/32) of the controls (odds ratio (OR) 4.33, 95% confidence interval (CI) 1.17–16.68). The infection was not associated with drinking unboiled water or any food items (Table 2). A habit of hand-washing (defined as at least once daily) was reported by 45.45% (10/22) of cases vs. 78.13% (25/32) of controls (OR 0.23, 95% CI 0.06–0.88). The daily frequency of hand-washing was inversely associated with infection (trend Chi-square = 5.35, $p = 0.021$) (Table 3).

3.3. Immunization records and immunological survey

Only two subjects claimed to have had prior HAV vaccination, but they could not provide any documents. No prior hepatitis A episode was reported in any of the children. The HAV IgM and HAV IgG positive rates in serum were 23.66% (22/93) and 41.94% (39/93), respectively. Serum HAV IgG antibody was detected in 46 out of the 47 (97.87%) consenting adult residents (Table 4).

3.4. Virological and bacteriological investigations

Both total coliform bacteria and fecal coliforms were >100 most probable number per 100 milliliters in all five water samples (the state requirement was not detectable[18]). However, no HAV was detected in drinking water or any food item.

3.5. Control measures for the outbreak

The following measures were taken within 24 h after the report by the Xinjian Center for Disease Control and Prevention: (1) isolation, hospitalization, and treatment of the symptomatic cases, (2) isolation and survey of the asymptomatic infection cases (within households), (3) disinfection of the water supply and sewage for 1 month despite the lack of evidence of these as the source of infection, (4) hygiene education, (5) injecting immune

Table 1
Age- and sex-specific attack rates of hepatitis A virus infection per hundred of the age group

Age, years	Male			Female			Total	
	Cases	Number of individuals	Rate (%)	Cases	Number of individuals	Rate (%)	Cases	Rate (%)
0–5	5	19	26.32	2	9	22.22	7	25.00
6–10	3	17	17.65	3	14	21.43	6	19.35
11–15	7	25	28.00	2	9	22.22	9	26.47
Total	15	61	24.59	7	32	21.88	22	23.66

Table 2
Risk factors for hepatitis A virus infection

Item	Number		%		OR	95% CI	*p*-Value
	Cases	Controls	Cases	Controls			
Close contact with infected persons	13	8	59.09	25	4.33	1.17–16.68	0.012
Drinking unboiled water	19	28	86.36	87.5	0.9	0.15–5.88	0.903
Snacks ('latiao')	18	31	81.82	96.88	0.15	0.01–1.58	0.061
Popsicle	19	29	86.36	90.63	0.98	0.12–9.44	0.986
Fruit	15	25	68.18	78.13	0.60	0.15–2.41	0.413
Habit of hand-washing	10	25	45.45	78.13	0.23	0.06–0.88	0.014

OR, odds ratio; CI, confidence interval.

Table 3
Hand-washing vs. hepatitis A virus infection[a]

Daily frequency of hand-washing	Number		%		OR	95% CI	*p*-Value
	Cases	Controls	Cases	Controls			
1–2	6	4	60	16	Ref.		
3–4	2	9	20	36	0.15	0.01–1.47	0.049
≥5	2	12	20	48	0.11	0.01–1.05	0.019

OR, odds ratio; CI, confidence interval.
[a]Chi-square for trend: Chi-square = 5.348, $p = 0.021$.

Table 4
Anti-HAV seropositive rate in Yujia Village of Xinjian County

	Age group, years				
	0–	5–	10–	>15	Total
Number of persons tested	28	31	34	47	140
Number positive for IgM	6	7	9	0	22
Positive rate for IgM (%)	21.43	22.58	26.47	0	15.71
Number positive for IgG	8	15	16	46	85
Positive rate for IgG (%)	28.57	48.39	47.06	97.87	60.71

Anti-HAV, antibody to hepatitis A virus.

serum globulin (ISG) to all residents with negative anti-HAV IgG or not inspected in the village, (6) hepatitis A vaccination for school-aged children in nearby villages, (7) postponing the scheduled opening of the village primary school by 1 month, and (8) an enhanced hepatitis A case survey in Xinjian County. No new case was reported after August 28 (one new case was reported on August 28). The outbreak was controlled using several control measures.

4. Discussion

Hepatitis A has a worldwide distribution and epidemics show a 7-yearly peak cycle similar to that of measles.[19] It is strongly correlated with socioeconomic factors; in developing countries with poor living conditions such as an inadequate water supply, poor sewage facilities, and substandard sanitary conditions, the level of HAV transmission within the community is high.[20] Until substantial improvements are made to the basic socioeconomic conditions, it is unrealistic to expect that universal vaccination will interrupt the chain of transmission in the general population via enhancing herd immunity. Although, the Chinese Ministry of Health included HAV vaccination in its expanded program of immunization (EPI) in 2008, outbreaks of hepatitis A in teenagers are still reported frequently. Most of the epidemic curves are typical of a common source or point source epidemic.

The epidemic curve in this outbreak showed four peaks, and the interval between peaks was about one average incubation period for hepatitis A, suggesting a person-to-person transmission pattern. Furthermore, the transmission chain of the symptomatic cases showed their relationship. No party event was identified to have occurred within the past 2 months. The majority of the food items (such as snacks and popsicles) shared by the children were purchased outside the village, and no cases of infection were reported outside the village during the outbreak period. The water supply system in the village is dispersed. This case–control study demonstrated that close contact with patients or asymptomatic cases was a major risk factor, whereas hand-washing was a protective factor.

Information bias may exist in this study. The investigation of cases and controls may have been impacted by recall bias because of the long latent period of hepatitis A. The questionnaires of the younger cases were completed by the parents, and thus may not reflect the real story. The date of infection among the asymptomatic cases could not be confirmed, but we should not exclude the possibility of transmission. Additionally, we did not conduct quantitative RT-PCR tests for the water samples because of time pressures and limited resources.

In summary, we failed to find any evidence of a common water source or food item as the source of this hepatitis A outbreak. The temporal pattern and close contact among the infection cases suggests fecal–oral transmission. For the control and prevention of hepatitis A outbreaks, we suggest the following: (1) improvements to the sensitivity of infectious disease surveillance (including hepatitis A) in rural areas, and the timely isolation and treatment of cases, (2) strengthening of hepatitis A vaccination in the school-aged population, (3) strengthening of the management of rural environmental sanitation, (4) the provision of safe food and water, and (5) strengthening health education to improve awareness of infectious disease prevention.

Acknowledgements

The authors thank Haiyin Chen, Hui Yuan, Huijian Cheng, Ying Xiong, Zheng Liao, Weijie Fu, Jincheng Qi, Wei Luo, and Weiguo Chen for their valuable advice and assistance during this investigation.

Funding: This study was supported by Jiangxi provincial financial funds for acute infectious disease prevention and control (8090108, http://www.jxjsw.gov.cn/). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest: The authors declare that they have no conflict of interest.

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